CLAIMS

What is claimed is:

1. A method for preparing a composition for the sustained release of a labile agent, comprising the steps of:
   a) forming a suspension comprising the labile agent dispersed in a polymer solution comprising at least one biocompatible polymer and at least one polymer solvent;
   b) wet milling the suspension to achieve submicron particles of the labile agent; and
   c) removing the polymer solvent thereby forming a solid polymer/labile agent matrix.

2. The method of Claim 1 wherein the submicron particles have a volume median particle size of less than 1 micron, measured by laser diffraction.

3. The method of Claim 1 wherein step (b) is conducted at a temperature of less than about 30°C.

4. The method of Claim 3 wherein the temperature is less than about 10°C.

5. The method of Claim 3 wherein the temperature is less than about 4°C.

6. The method of Claim 1 wherein the labile agent is present in the suspension at a concentration of from about 0.01 to about 50% w/w of the combined weight of polymer and labile agent.

7. The method of Claim 6 wherein the labile agent is present at a concentration of about 0.01 to 30% w/w of the combined weight of the polymer and labile agent.

8. The method of Claim 1 wherein the labile agent is a protein, polypeptide or oligonucleotide.

9. The method of Claim 1 wherein the labile agent is a protein.

10. The method of Claim 8 wherein the labile agent is complexed to a stabilizing metal cation.

11. The method of Claim 10 wherein said stabilizing metal cation is selected from the group consisting of Zn^{+2}, Ca^{+2}, Cu^{+2}, Mg^{+2}, K^{+} and any combination thereof.

12. The method of Claim 11 wherein said stabilizing metal cation is Zn^{+2}.

13. The method of Claim 10 wherein the labile agent is human growth hormone.

14. The method of Claim 13 wherein the human growth hormone is complexed to Zn^{+2}.

15. The method of Claim 1 wherein the biocompatible polymer is biodegradable.

16. The method of Claim 15 wherein the biodegradable polymer is selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-coglycolide)s, poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, poly(caprolactone), polycarbonates, polyesteramides, polyanhydrides, poly(amino acid)s, poly(ortho ester)s, polycyanoacrylates, polyamides,

polyacetals, poly(ether ester)s, copolymers of poly(ethylene glycol) and poly(ortho ester)s, poly(dioxanone)s, poly(alkylene alkylate)s, biodegradable polyurethanes, blends and copolymers thereof.

17. The method of Claim 16 wherein said polymer is poly(lactide-co-glycolide).

18. The method of Claim 15 wherein the biocompatible polymer is non-biodegradable.

19. The method of Claim 1 wherein the polymer solvent is methylene chloride, chloroform, acetone, ethyl acetate, methyl acetate, dimethylsulfoxide, hexafluoroisopropanol or any combinations thereof.

20. The method of Claim 1 wherein the composition for sustained release further comprises a metal cation component dispersed within the polymer wherein said metal cation component is added to the suspension after step (b) and before step (c), and which modulates the release of the labile agent.

21. The method of Claim 20 wherein the metal cation component is selected from the group consisting of $Mg(OH)_2$, $MgCO_3$, $CaCO_3$, $ZnCO_3$, $Mg(OAc)_2$, $Zn(OAc)_2$, $ZnSO_4$, $MgCl_2$, $ZnCl_2$, $MgSO_4$, zinc citrate and magnesium citrate.

22. A composition for the sustained release of a labile agent prepared by the method comprising the steps of:

a) forming a suspension comprising the labile agent dispersed in a polymer solution comprising at least one biocompatible polymer and at least one polymer solvent;

b) wet milling the suspension to achieve submicron particles of the labile agent; and

c) removing the polymer solvent thereby forming a solid polymer/labile agent matrix.

23. The composition of Claim 22 wherein the submicron particles have a volume median particle size of less than 1 micron, measured by laser diffraction.

24. The composition of Claim 22 wherein step (b) is conducted at a temperature of less than about 30°C.

25. The composition of Claim 24 wherein the temperature is less than about 10°C.

26. The composition of Claim 24 wherein the temperature is less than about 4°C.

27. The composition of Claim 22 wherein the labile agent is present in the suspension at a concentration of from about 0.01 to about 50% w/w of the combined weight of polymer and labile agent.

28. The composition of Claim 27 wherein the labile agent is present at a concentration of about 0.01 to 30% w/w of the combined weight of the polymer and labile agent.

29. The composition of Claim 22 wherein the labile agent is a protein, polypeptide or oligonucleotide.

30. The composition of Claim 22 wherein the labile agent is a protein.

31. The composition of Claim 29 wherein the labile agent is complexed to a stabilizing metal cation.

32. The composition of Claim 31 wherein said stabilizing metal cation is selected from the group consisting of Zn^{+2}, Ca^{+2}, Cu^{+2}, Mg^{+2}, K^{+} and any combination thereof.

33. The composition of Claim 32 wherein said stabilizing metal cation is Zn^{+2}.

34. The composition of Claim 31 wherein the labile agent is human growth hormone.

35. The composition of Claim 34 wherein the human growth hormone is complexed to Zn^{+2}.

36. The composition of Claim 22 wherein the biocompatible polymer is biodegradable.

37. The composition of Claim 36 wherein the biodegradable polymer is selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-coglycolide)s, poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, poly(caprolactone), polycarbonates, polyesteramides, polyanhydrides, poly(amino acid)s, poly(ortho ester)s, polycyanoacrylates, polyamides, polyacetals, poly(ether ester)s, copolymers of poly(ethylene glycol) and poly(ortho ester)s, poly(dioxanone)s, poly(alkylene alkylate)s, biodegradable polyurethanes, blends and copolymers thereof.

38. The composition of Claim 37 wherein said polymer is poly(lactide-co-glycolide).

39. The composition of Claim 22 wherein the biocompatible polymer is non-biodegradable.

40. The composition of Claim 22 wherein the polymer solvent is methylene chloride, chloroform, acetone, ethyl acetate, methyl acetate, dimethylsulfoxide, hexafluoroisopropanol or any combinations thereof.

41. The composition of Claim 41 wherein the metal cation component is selected from the group consisting of $Mg(OH)_2$, $MgCO_3$, $CaCO_3$, $ZnCO_3$, $Mg(OAc)_2$, $Zn(OAc)_2$, $ZnSO_4$, $MgCl_2$, $ZnCl_2$, $MgSO_4$, zinc citrate and magnesium citrate.